Updated 7/28/02

FILE 'CAPLUS, BABS, CBNB, CEN, CIN, DKILIT, IFIPAT, JICST-EPLUS, PASCAL, PLASNEWS, PROMT, RAPRA, SCISEARCH, TEXTILETECH, USPATFULL, USPAT2, WPIDS, WTEXTILES' ENTERED AT 16:52:11 ON 28 JUL 2002

| | | |
|---|---|---|
| L1 | 76425 | S SOL(W)GEL |
| L2 | 6631 | S L1 AND GLASSES |
| L3 | 1062 | S L2 AND SYNTHESIS |
| L4 | 26 | S L3 AND ALKOXYSILANES |
| L5 | 23 | S L4 AND METAL |
| L6 | 22 | S L5 AND ORGANIC |

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L1       76425 SOL(W) GEL

=> s L1 and glasses
L2        6631 L1 AND GLASSES

=> s L2 and synthesis
L3        1062 L2 AND SYNTHESIS

=> s L3 and alkoxysilanes
L4          26 L3 AND ALKOXYSILANES

=> s l4 and metal
L5          23 L4 AND METAL

=> s L5 and organic
L6          22 L5 AND ORGANIC
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L6 ANSWER 8 OF 22 USPATFULL
AN 1998:128118 USPATFULL
TI Doped **sol-gel glasses** for obtaining chemical interactions
IN Avnir, David, Jerusalem, Israel
Ottolenghi, Michael, Jerusalem, Israel
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PA YISSUM, Research Development Company of the Hebrew University of Jerusalem, Israel, Jerusalem, Israel (non-U.S. corporation)
PI US 5824526 19981020
AI US 1996-667746 19960621 (8)
RLI Continuation of Ser. No. US 1994-266441, filed on 28 Jun 1994, now patented, Pat. No. US 5650311 which is a continuation of Ser. No. US 1992-937259, filed on 31 Aug 1992, now abandoned which is a division of Ser. No. US 1991-637873, filed on 8 Jan 1991, now patented, Pat. No. US 5300564
PRAI IL 1990-93134 19900123
DT Utility
FS Granted
LN.CNT 629
INCL INCLM: 435/176.000
INCLS: 252/315.600; 252/408.100; 424/484.000; 428/402.240; 436/527.000; 501/012.000; 514/944.000; 514/965.000; 530/811.000
NCL NCLM: 435/176.000
NCLS: 252/408.100; 424/484.000; 428/402.240; 436/527.000; 501/012.000; 514/944.000; 514/965.000; 516/111.000; 530/811.000
IC [6]
ICM: G01N001-00
ICS: A61K009-50; B01J013-18
EXF 252/183.13; 252/184; 252/315.6; 252/408.1; 428/402.24; 501/12; 065/21.1; 436/169; 436/527; 210/498; 210/500.26; 422/238; 422/239; 435/176; 424/484; 514/944; 514/965; 530/811
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Doped **sol-gel glasses** for obtaining chemical interactions
AB A **sol-gel** glass doped with one or more reagent that provides chemical interactions with diffusible solutes or components in an adjacent liquid or gas phase. The reagent(s), the solutes or the components can be any **organic** or inorganic compounds or materials of biological origin, including enzymes. The doped **sol-gel** glass in various forms is useful as an analytical test, chromatographic medium, sensor, catalyst or biocatalyst, electrode or enzyme electrode,. . .
SUMM . . . solid support and diffusible solutes or components in an adjacent liquid or gas phase, wherein said reagent/s are trapped in **sol-gel** glass (hereinafter also referred to as doped **sol-gel** glass) which provides the solid support to the reagent/s.
SUMM The method according to the present invention can be applied to a variety of interactions between the doped **sol gel glasses** and reagent/s in an adjacent liquid or gas phase. The present invention can be useful in a myriad of applications:. . . useful for detection of ions by chemical interaction between the ion/s in an aqueous phase and reagents trapped in the "**sol-gel**" glass, or vice versa, via characteristic "color test" reactions, or other routine detection methods. Another example is utilization of the. . .
SUMM The method can be applied as well for medical diagnostic purposes e.g. for detecting inorganic ions and/or small **organic** molecules in blood, urine and other body liquids. Another example, according to the

present invention, is a chemical interaction between a substrate/antigen in the liquid phase and an enzyme/antibody trapped in the "**sol -gel**" glass.

SUMM For centuries, inorganic **glasses** have been prepared by high temperature melting methods. This has imposed a major limitation upon the technological application of **glasses**: additives were restricted to thermally stable inorganic materials, while precluding the incorporation of labile **organic** molecules.

SUMM A recent major development in material science has been the preparation of inorganic (silica) **glasses** through the low temperature "**sol-gel" synthesis** (Brinker, C. J., Scherer, G. W., **Sol-Gel** Science, Academic Press, San Diego (1990)). An amorphous bond network of the glassy material is prepared by the room-temperature polymerization of suitable monomers, usually **metal** alkoxides, according to schemes such as:

SUMM By **sol-gel** glass one also means the product obtained by a polymerization of **metal** alkoxide mixtures which bear both hydrolyzable and nonhydrolyzable substituents.

SUMM The low-temperature glass **synthesis** allows doping inorganic (silica or other) **glasses**, with essentially any **organic** molecule. This possibility was used for trapping of e.g. photoactive molecules by adding the compound to the starting mixture at. . . R., J. Phys. Chem. 88, 5956 (1984)). The compound remained permanently trapped, i.e. non-leachable system have been obtained. These doped **sol-gel glasses** have been used as photoactive materials, such as:

SUMM (d) Photochromic and phosphorescent **glasses**.

SUMM . . . such parameters as porosity, water content and degree of (cage) polarity (Kaufman, V. R., Avnir, D., Structural changes Along the **Sol-Gel**-Xerogel Transitions, Langmuir 2, 717 (1986); Kaufman, V. R., Avnir, D., Pines-Rojanski, D., Huppert, D., Water Consumption During the Early Stages of the **Sol-Gel** Polymerization, J. Non-Cryst. Solids 99, 379 (1988)).

SUMM **Sol-gel glasses** demonstrate several technologically attractive properties:

SUMM Surprisingly, it was found that molecules trapped in **sol gel glasses**, may interact with diffusible solutes or components in an adjacent liquid or gas phase in the pore space. Said finding opened a new wide range of applications of doped **sol-gel glasses** as solid media for chemical interactions.

SUMM . . . support and diffusible solute/s or component/s in an adjacent liquid or gas phase, wherein said reagent/s are trapped in the **sol-gel** glass which serves as the solid support. Said reagent/s can be any **organic** compound, organometallic, or inorganic compound, or any biological material capable of being trapped in the **sol-gel** glass.

SUMM The diffusible solute/s or components can be any **organic** compound, stable **organic** radical, organometallic, or inorganic compound or biological material capable to interact with the trapped reagents.

SUMM . . . present invention can take place between anions or cations in a liquid or gas phase and reagents trapped in the **sol gel** glass or vice versa. For example the interaction may take place between **metal** ions and a specific reagents via a characteristic colour-test reaction, as in: (1) the determination of Fe.sup.+2 cation with o-phenanthrolin,. . . is one of many examples for a pH sensors. The analytical test can be carried out by dipping the doped **sol gel** glass in the solution and observing the resulting color change.

SUMM The **sol gel** glass according to the present invention can be in any shape suitable for the test. For example it can have. . . inert solid support. Thus, an electrochemical test according to said

invention can be performed by preparing electrodes coated with doped **sol gel** glass layers. These electrodes may be used for clinical, analytical or industrial purpose, or as biosensors.

SUMM . . . quantitative analysis of pollutants. Said pollutants may be for example chlorides, nitrates, phosphates, herbicides, insecticides, inorganic ions and pollutants of **organic** origin. Detection devices according to this invention can be utilized as a part of continuous monitoring systems.

SUMM The present invention can be utilized for extracting or separating molecular solutes from liquid solutions. The doped **sol gel glasses** can be used according to the present invention for all chromatographic purposes, including liquid, gas and thin layer chromatography. The extraction or separation is performed by passing the solution through columns made from appropriately doped **sol gel** material. The thin layer chromatography according to this invention can be performed on conventional glass plates, paper or other inert solid support coated with doped **sol -gel** glass layers.

SUMM Medical diagnostic is another application of the present invention. For example, detection of inorganic ions, small **organic** molecules and other components in blood, urine and other body liquids. The invention can be applied also to the fractionation. . .

SUMM . . . invention relates, as well, to a method for preparation of bioactive materials (biocatalysts) by entrapment of enzymes in a forming **sol-gel** glass, which, following polycondensation of suitable monomers, serves as a solid matrix, bonding the enzyme and conveying to it mechanical,. . .

SUMM . . . according to the present invention, can be applied to a variety of enzymes or enzyme systems, including co-immobilization of co-factors, **organic** and inorganic ligands, mono- and polyclonal antibodies, and their detection systems.

SUMM . . . the present invention can be useful in a variety of applications, such as: (a) biochemical reactions and other bioconversions in **organic** and inorganic solvent solutions, (b) detection or qualitative determination of **organic** and inorganic molecules, which are substrates of the immobilized enzymes, or inhibitors, or modifiers of enzyme activity, (c) construction of. . .

SUMM Several properties of the **sol-gel glasses** make them especially attractive as possible enzyme catalyst supports: (a) the ability to entrap large amounts of additives; (b) the. . .

SUMM . . . also to a method for obtaining bioactive materials based on an enzyme molecules trapped within the porous structure of a **sol-gel** glass. The entrapment is achieved by the addition of a cell-free enzyme to a mixture of monomer or monomers at. . .

SUMM Unexpectedly, we have found (1) that proteins can be trapped within the matrix of a forming **sol-gel**, (2) that several cell-free enzymes, belonging to various classes: hydrolases, oxidoreductases, lyases etc., can be effectively entrapped in such composite bioactive **sol-gel glasses**, while retaining high enzymatic activity, (3) that strong binding forces retain the enzyme in the matrix, thus producing a considerable. . .

SUMM The **sol-gel** immobilized enzymes may be used as biosensors for hormonal tests or for any industrial purposes, including diagnostic and synthetic purposes. Said enzymes can be doped in **sol gel** glass layers coated on electrodes for probing any substrate. The enzymatic interaction according to the present invention can be applied also to radioactive tests and also for enzymatic column chromatography (crushed powder **sol gel glasses** may be used as support for enzymatic column chromatography).

SUMM The **sol gel** glass can be applied, according to the present invention, as active specific membranes allowing selective

incorporation of the trapped molecules. . .

SUMM The present invention relates also to the application of doped **sol gel glasses** according to this invention as well as for the preparation of **sol gel glasses** and doped **sol gel glasses** for such applications.

SUMM When prepared as thin film the width of the **sol gel** glass may be from molecular monolayers up to macroscopic layers. Said thin film can be part of multi-layered array of thin films. Said **glasses** may be supported on an electrode or optical support.

SUMM The unique transparency of **"sol gel" glasses** in the range above 250 nm, makes them highly applicable to quantitative spectrophotometric and spectrofluorimetric tests. Trapping of host molecules. . . require specific synthetic methods such as those associated with covalent linking of reagents to solid supports. Moreover, inherent properties of **sol gel glasses** such as high surface area, the wide range of available pore sizes and the thin film technology, make them highly. . .

DRWD The FIGURE drawing shows various **glasses** with a reagent trapped therein, both before and after reaction with a component in the liquid phase.

DETD A. Preparation of doped **"sol-gel" glasses**

DETD The polycondensation of **alkoxysilanes** is associated with gelation of the sol, which after drying is densified by a mild heat treatment to form a. . . final glass are determined by the chemical and physical conditions during the process of preparation. They depend upon the ratio **metal** (e.g. silane)/alcohol/water, the alkoxide pH, the presence of a catalyst, the temperature, the drying time and the amounts of **organic** additives, such as surface active agents.

DETD 1. A standard mixture for preparation of doped **"sol-gel" glasses** contained TMOS (5 ml) H.sub.2 O (2.4 ml) and methanol (6. ml). The appropriate catalyst and the desired reagent were. . .

DETD 2. An alternative technique of preparing **sol-gel glasses** is based on thin-layer coating of conventional glass supports. A characteristic procedure for the preparation of such thin layers began. . .

DETD B. Representative examples of reactivity of reagents trapped in **sol-gel glasses**

DETD . . . to the same glass after immersion in the tested solution. The doped glasse.ltoreq.represent four classes of reactions: (a) a glass-trapped **organic** reagent with an inorganic cation to be determined in the solution; (b) same with inorganic anions; (c) a glass doped with an inorganic ion, testing a solution containing an **organic** molecule (reversal of a & b); (d) glass doped with a pH indicator.

DETD Middle: Doped **glasses** (top) and some **glasses** after immersion in solutions containing several ions:

DETD 1. Preparation of **sol-gel** immobilized enzymes.

DETD All the liquid remaining on the top of **sol-gel** was then removed by suction. In methanol-containing mixtures gelation took place in about 4-5 h. The polymerized sol was allowed. . .

DETD 2. Retention of protein by the **sol-gel** glass.

DETD All the **glasses** prepared according to example C1 were ground to a size of about 60-100 mesh and packed in 2 ml-columns. The. . .

DETD 3. Entrapment of trypsin in **sol-gel glasses**

.

DETD Trypsin (E.C. 3.4.21.4, from bovine pancreas, 11,000 U/mg) was supplied by RAD Chemicals, Rehovot, Israel. Trypsin entrapped in **sol-gel** was prepared as described in example C1. Assays were performed on the washed **glasses** at 25.degree. C. at pH 8 using n-benzoyl-L-arginine-4-nitroanilide (3.3 mM) as the substrate. The

concentration of NaF in the enzyme. . .

DETD 4. Entrapment of acid phosphatase in **sol-gel glasses**.

DETD Acid phosphatase (E.C. 3.1.3.2, from wheat germ, 0.45 U/mg) was purchased from Sigma. The acid phosphatase-containing **sol-gel glasses** were prepared as described in the example C1. The assays were performed on the washed **glasses** at 25.degree. C. at pH 5.6 using p-nitrophenyl phosphate (6 mM) as the substrate. The activity yield, calculated in percents of enzyme activity used initially for the preparation of **glasses**, is shown in the following Table:

DETD 5. Thermal stability of immobilized acid phosphatase in different **sol-gel glasses**.

DETD The acid phosphatase-containing **sol-gel glasses** (example C4) were incubated at 70.degree. C. in citrate buffer (pH 5.6, 0.1M) for various periods of time (up to. . .

DETD 6. Entrapment of peroxidase in **sol-gel glasses**.

DETD . . . 200 U/mg) was obtained from Sigma. Sol-gels doped with peroxidase were prepared as shown in the example C1. All the **glasses** prepared with the addition of PEG 400 were active, although it was not possible to determine the extent of their. . . of the assay mixture indicated improved activity yields at higher concentrations of PEG 400. In contrast to trypsin and catalase, **sol-gel glasses** made at elevated concentrations of NaF were more active. **Glasses** prepared in methanol-containing mixtures were devoid of peroxidase activity.

DETD 7. Entrapment of trypsin in **sol-gel glasses**

.

DETD . . . to reach the room temperature. The polymerized sol was allowed to dry for a week at 30.degree. C. The resulting **glasses** were treated as described (example C2). Trypsin activity of the trypsin-doped **sol-gel glasses** expressed as the yield of activity used for the preparation of the catalyst is presented in the following Table.

DETD 8. Entrapment of aspartase in **sol-gel glasses**.

DETD . . . disrupted by sonication. The homogenate was cleared by centrifugation (10,000.times.g, 30 min, 4.degree. C.) and used for the preparation of **sol-gel glasses**. The homogenate (0.5 ml) was mixed with NaF solution (0.2 ml) at the concentrations indicated in the Table below. Methanol. . .

DETD 9. Preparation of protein-doped **glasses** by NaOH catalyzed polycondensation. Immobilization of alkaline phosphatase.

DETD . . . pathological conditions, and may thus be of significant prognostic value. We have used an Anti-IL-2R monoclonal antibody, trapped in a **sol-gel** glass, to determine IL-2R, using a sandwich immuno assay test (cell-free Interleukin-2 Receptor CK 1020, 96 Test kit, T Cell Sciences, Inc., Cambridge, Mass., USA). Trapping of Anti-IL-2R monoclonal antibody in a "**sol-gel**" glass was carried out with a starting solution composed of methanol (3 ml), TMOS (2.5 ml), 6 mM phosphate buffered. . .

CLM What is claimed is:

1. A reactive **sol-gel** comprising a porous solid gel containing a chemically reactive cell-free dopant of biological origin trapped therein and formed by non-denaturing polymerization of at least one monomer of the formula M(R).sub.n (P).sub.m and selected from the group consisting of **metal** alkoxides, semi-**metal** alkoxides, **metal** esters and semi-**metal** esters, wherein M is a metallic or semi-metallic element, R is a hydrolyzable substituent, n is an integer of 2. . .

2. A reactive **sol-gel** as defined by claim 1, wherein

the porous solid gel is in the form of a rod, a disc, a. . .
3. A reactive **sol-gel** as defined by claim 2, wherein
the porous solid gel is a thin film in the form of a molecular. . .
4. A reactive **sol-gel** as defined by claim 2, wherein
the porous solid gel is a thin film in the form of a macroscopic. . .
5. A reactive **sol-gel** as defined by claim 2, wherein
the porous solid gel is a thin film and is supported on a solid. . .
6. A reactive **sol-gel** as defined by claim 1, wherein
the porous gel is in the form of thin sieves.

7. A reactive **sol-gel** as defined by claim 1, wherein
at least two dopants are trapped in the porous solid gel and wherein
the. . .
8. A reactive **sol-gel** as defined by claim 1, wherein
the distribution of dopant in the gel is nonhomogeneous and follows a
predetermined gradient.
. . .
9. A reactive **sol-gel** as defined by claim 1, wherein
the cell-free dopant of biological origin is a protein.

10. A reactive **sol-gel** as defined by claim 9,
wherein the cell-free dopant is selected from the group consisting of
enzymes, monoclonal antibodies and. . .
11. A reactive **sol-gel** as defined by claim 10,
wherein the cell-free dopant is an enzyme.

L6 ANSWER 12 OF 22 USPATFULL
AN 97:63914 USPATFULL
TI Doped **sol-gel glasses** for obtaining
chemical interactions
IN Avnir, David, Jerusalem, Israel
Ottolenghi, Michael, Jerusalem, Israel
Braun, Sergei, Jerusalem, Israel
Zusman, Rivka, Jerusalem, Israel
PA Yissum, Research Development Company of the Hebrew University of
Jerusalem, Israel, Jerusalem, Israel (non-U.S. corporation)
PI US 5650311 19970722
AI US 1994-266441 19940628 (8)
RLI Continuation of Ser. No. US 1992-937259, filed on 31 Aug 1992, now
abandoned which is a division of Ser. No. US 1991-637873, filed on 8 Jan
1991, now patented, Pat. No. US 5300564
PRAI IL 1990-93134 19900123
DT Utility
FS Granted
LN.CNT 614
INCL INCLM: 435/176.000
INCLS: 252/315.600; 252/408.100; 424/484.000; 428/402.240; 436/527.000;
501/012.000; 514/944.000; 514/965.000; 530/811.000
NCL NCLM: 435/176.000
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514/944.000; 514/965.000; 516/098.000; 516/111.000; 516/112.000;
530/811.000
IC [6]
ICM: G01N001-00
ICS: A61K009-50; B01J013-18
EXF 252/183.13; 252/184; 252/315.6; 252/408.1; 428/402.24; 501/12; 065/21.1;
436/169; 436/527; 210/498; 210/500; 210/26; 422/238; 422/239; 435/176;
424/484; 514/944; 514/965; 530/811
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Doped **sol-gel glasses** for obtaining
chemical interactions

AB A metod is proposed of obtaining a chemical interaction between at least one reagent trapped in **sol-gel** glass by doping it with the reagent(s), and diffusible solutes or components in an adjacent liquid or gas phase. The reagents, the solutes or the components can be any **organic** or inorganic compounds or materials of biological origins including enzymes. The doped **sol-gel** glass in various forms may be useful as analytical test, chromatographic medium, sensor, catalyst or biocatalyst, electrode or enzyme electrode,. . .

SUMM . . . solid support and diffusible solutes or components in an adjacent liquid or gas phase, wherein said reagent/s are trapped in **sol-gel** glass (hereinafter also referred to as doped **sol-gel** glass) which provides the solid support to the reagent.

SUMM The method according to the present invention can be applied to a variety of interactions between the doped **sol gel glasses** and reagent in an adjacent liquid or gas phase. The present invention can be useful in a myriad of applications:. . . useful for detection of ions by chemical interaction between the ions in an aqueous phase and reagents trapped in the "**sol-gel** " glass, or vice versa, via characteristic "color test" reactions, or other routine detection methods. Another example is utilization of the. . .

SUMM The method can be applied as well for medical diagnostic purposes e.g. for detecting inorganic ions or small **organic** molecules in blood, urine and other body liquids. Another example, according to the present invention, is a chemical interaction between a substrate or antigen in the liquid phase and an enzyme or antibody trapped in the " **sol-gel**" glass.

SUMM For centuries, inorganic **glasses** have been prepared by high temperature melting methods. This has imposed a major limitation upon the technological application of **glasses**: additives were restricted to thermally stable inorganic materials, while precluding the incorporation of labile **organic** molecules.

SUMM A recent major development in material science has been the preparation of inorganic (silica) **glasses** through the low temperature " **sol-gel" synthesis** (as disclosed by Brinker, C. J., Scherer, G. W., **Sol-Gel** Science, Academic Press, San Diego (1990). An amorphous bond network of the glassy material is prepared by the room-temperature polymerization of suitable monomers, usually **metal** alkoxides, according to schemes such as:

SUMM By **sol-gel** glass one also means the product obtained by a polymerization of **metal** alkoxide mixtures which bear both hydrolyzable and nonhydrolyzable substituents. The monomers may also comprise **metal** esters, semi-**metal** esters, or semi-**metal** alkoxides, with preferred metals or semi-metals comprising Si, Al, Ti or Pb.

SUMM The low-temperature glass **synthesis** allows doping of inorganic (silica or other) **glasses**, with essentially any **organic** molecule. This possibility was used for trapping of photoactive molecules by adding the compound to the starting mixture at the. . . R., J. Phys. Chem. 88, 5956 (1984)). The compound remained permanently trapped, i.e. non-leachable system have been obtained. These doped **sol-gel glasses** have been used as photoactive materials, such as:

SUMM (d) Photochromic and phosphorescent **glasses**.

SUMM . . . such parameters as porosity, water content and degree of (cage) polarity (Kaufman, V. R., Avnir, D., Structural changes Along the **Sol-Gel**-Xerogel Transitions, Langmuir 2, 717 (1986); Kaufman, V. R., Avnir, D., Pines-Rojanski, D., Huppert, D., Water Consumption During the Early Stages of the **Sol-Gel**

Polymerization, J. Non-Cryst. Solids 99, 379 (1988)).

SUMM **Sol-gel glasses** demonstrate several technologically attractive properties:

SUMM Surprisingly, it was found that molecules trapped in **sol gel glasses**, may interact with diffusible solutes or components in an adjacent liquid or gas phase in the pore space. This finding opened a new wide range of applications of doped **sol-gel glasses** as solid media for chemical interactions.

SUMM . . . least one diffusible solute or component in an adjacent liquid or gas phase, wherein the reagent is trapped in the **sol-gel** glass which serves as the solid support. The reagent can be any **organic** organometallic, or inorganic compound, or any biological material capable of being trapped in the **sol-gel** glass.

SUMM The diffusible solute or components can be any **organic** compound, stable **organic** radical, organometallic compound, or inorganic compound or biological material capable to interact with the trapped reagents.

SUMM . . . present invention can take place between anions or cations in a liquid or gas phase and reagents trapped in the **sol gel** glass or vice versa. For example the interaction may take place between **metal** ions and a specific reagent via a characteristic colour-test reaction, as in: (1) the determination of Fe.sup.+2 cation with o-phenanthrolin,. . . is one of many examples for a pH sensors. The analytical test can be carried out by dipping the doped **sol gel** glass in the solution and observing the resulting color change.

SUMM The **sol gel** glass according to the present invention can be in any shape suitable for the test. For example it can have. . . inert solid support. Thus, an electrochemical test according to the invention can be performed by preparing electrodes coated with doped **sol gel** glass layers. These electrodes may be used for clinical, analytical or industrial purpose, or as biosensors.

SUMM . . . quantitative analysis of pollutants. The pollutants may be for example chlorides, nitrates, phosphates, herbicides, insecticides, inorganic ions and pollutants of **organic** origin. Detection devices according to this invention can be utilized as part of continuous monitoring systems.

SUMM The present invention can be utilized for extracting or separating molecular solutes from liquid solutions. The doped **sol gel glasses** can be used according to the present invention for all chromatographic purposes, including liquid, gas and thin layer chromatography. The extraction or separation is performed by passing the solution through columns made from appropriately doped **sol gel** material. The thin layer chromatography according to this invention can be performed on conventional glass plates, paper or other inert solid support coated with doped **sol-gel** glass layers.

SUMM Medical diagnostics is another application of the present invention. For example, detection of inorganic ions, small **organic** molecules and other components in blood, urine and other body liquids can be made. The invention can be applied also. . .

SUMM . . . present invention relates, as well, to a method for preparation of bioactive materials (biocatalysts) by entrapment of enzymes in forming **sol-gel** glass, which, following polycondensation of suitable monomers, serves as a solid matrix, bonding the enzyme and conveying to it mechanical,. . .

SUMM . . . according to the present invention, can be applied to a variety of enzymes or enzyme systems, including co-immobilization of co-factors, **organic** and inorganic ligands, mono- and polyclonal antibodies, and their detection systems.

SUMM . . . the present invention can be useful in a variety of

applications, such as: (a) biochemical reactions and other bioconversions in **organic** and inorganic solvent solutions, (b) detection or qualitative determination of **organic** and inorganic molecules, which are substrates of the immobilized enzymes, or inhibitors, or modifiers of enzyme activity, (c) construction of. . .

SUMM Several properties of the **sol-gel glasses** make them especially attractive as possible enzyme catalyst supports: (a) the ability to entrap large amounts of additives; (b) the. . .

SUMM . . . therefore also to a method for obtaining bioactive materials based on enzyme molecules trapped within the porous structure of a **sol-gel** glass. The entrapment is achieved by the addition of a cell-free enzyme to a mixture of monomer or monomers at. . .

SUMM Unexpectedly, we have found (1) that proteins can be trapped within the matrix of a forming **sol-gel**, (2) that several cell-free enzymes, belonging to various classes: hydrolases, oxidoreductases, lyases and the like, can be effectively entrapped in such composite bioactive **sol-gel glasses**, while retaining high enzymatic activity, and (3) that strong binding forces retain the enzyme in the matrix, thus producing a. . .

SUMM The **sol-gel** immobilized enzymes may be used as biosensors for hormonal tests or for any industrial purposes, including diagnostic and synthetic purposes. Said enzymes can be doped in **sol gel** glass layers coated on electrodes for probing any substrate. The enzymatic interaction according to the present invention can be applied also to radioactive tests and also for enzymatic column chromatography (crushed powder **sol gel glasses** may be used as support for enzymatic column chromatography).

SUMM The **sol gel** glass can be applied, according to the present invention, as active specific membranes allowing selective incorporation of the trapped molecules. . .

SUMM The present invention relates also to the application of doped **sol gel glasses** according to this invention as well as for the preparation of **sol gel glasses** and doped **sol gel glasses** for such applications.

SUMM When prepared as a thin film, the width of the **sol gel** glass may be from molecular monolayers up to macroscopic layers. The thin film can be part of a multi-layered array of thin films. The **glasses** may be supported on an electrode or optical support.

SUMM The unique transparency of **"sol gel" glasses** in the range above 250 nm, makes them highly applicable to quantitative spectrophotometric and spectrofluorimetric tests. Trapping of host molecules. . . require specific synthetic methods such as those associated with covalent linking of reagents to solid supports. Moreover, inherent properties of **sol gel glasses** such as high surface area, the wide range of available pore sizes and the thin film technology, make them highly. . .

DRWD The figure drawing shows various **sol-gel glasses** with a reagent trapped therein, both before and after reaction with a component in a liquid phase.

DETD A. Preparation of doped **"sol-gel" glasses**

DETD The polycondensation of **alkoxysilanes** associated with gelation of the sol, which after drying is densified by a mild heat treatment to form a glass.. . . final glass are determined by the chemical and physical conditions during the process of preparation. They depend upon the ratio **metal** (e.g. silane)/alcohol/water, the alkoxide pH, the presence of a catalyst, the temperature, the drying time and the amounts of **organic** additives, such as surface active agents.

DETD 1. A standard mixture for preparation of doped **"sol-gel" glasses** contained TMOS (5 ml) H.sub.2 O (2.4 ml)

and methanol (6. ml). The appropriate catalyst and the desired reagent were. . .

DETD 2. An alternative technique of preparing **sol-gel glasses** is based on thin-layer coating of conventional glass supports. A characteristic procedure for the preparation of such thin layers began. . .

DETD B. Representative examples of reactivity of reagents trapped in **sol-gel glasses**

DETD . . . 1, arrows denote transitions from the reagent-doped glass to the same glass after immersion in the tested solution. The doped **glasses** represent four classes of reactions: (a) a glass-trapped **organic** reagent with an inorganic cation to be determined in the solution; (b) same with inorganic anions; (c) a glass doped with an inorganic ion, testing a solution containing an **organic** molecule (reversal of a & b); (d) glass doped with a pH indicator.

DETD Middle: Doped **glasses** (top) and some **glasses** after immersion in solutions containing several ions:

DETD 1. Preparation of **sol-gel** immobilized enzymes.

DETD . . . samples containing PEG 400, the polymerization was completed in about 3 h. All the liquid remaining on the top of **sol-gel** was then removed by suction. In methanol-containing mixtures gelation took place in about 4-5 h. The polymerized sol was allowed. . .

DETD 2. Retention of protein by the **sol-gel** glass.

DETD All the **glasses** prepared accordin9 ko example C1 were ground to a size of about 60-100 mesh and packed in 2 ml-columns. The. . .

DETD 3. Entrapment of trypsin in **sol-gel glasses** .

DETD Trypsin (E.C. 3.4.21.4, from bovine pancreas, 11,000 U/mg) was supplied by RAD Chemicals, Rehovot, Israel. Trypsin entrapped in **sol-gel** was prepared as described in example C1. Assays were performed on the washed **glasses** at 25.degree. C. at pH 8 using N-benzoyl-L-arginine-4-nitroanilide (3.3 mM) as the substrate. The concentration of NaF in the enzyme. . .

DETD 4. Entrapment of acid phosphatase in **sol-gel glasses.**

DETD Acid phosphatase (E.C. 3.1.3.2, from wheat germ, 0.45 U/mg) was purchased from Sigma. The acid phosphatase-containing **sol-gel glasses** were prepared as described in the example C1. The assays were performed on the washed **glasses** at 25.degree. C. at pH 5.6 using p-nitrophenyl phosphate (6 mM) as the substrate. The activity yield, calculated percents of enzyme activity used initially for the preparation of **glasses,** is shown in the following Table:

DETD 5. Thermal stability of immobilized acid phosphatase in different **sol-gel glasses.**

DETD The acid phosphatase-containing **sol-gel glasses** (example C4) were incubated at 70.degree. C. in citrate buffer (pH 5.6, 0.1M) for various periods of time (up to. . .

DETD 6. Entrapment of peroxidase in **sol-gel glasses.**

DETD . . . 200 U/mg) was obtained from Sigma. Sol-gels doped with peroxidase were prepared as shown in the example C1. All the **glasses** prepared with the addition of PEG 400 were active, although it was not possible to determine the extent of their. . . of the assay mixture indicated improved activity yields at higher concentrations of PEG 400. In contrast to trypsin and catalase, **sol-gel glasses** made at elevated concentrations of NaF were more active. **Glasses** prepared in methanol-containing mixtures were devoid of peroxidase activity.

DETD 7. Entrapment of trypsin in **sol-gel glasses** .

DETD . . . to reach the room temperature. The polymerized sol was allowed to dry for a week at 30.degree. C. The resulting **glasses** were treated as described (example C2). Trypsin activity of the trypsin-doped **sol-gel glasses** expressed as the yield of activity used for the preparation of the catalyst is presented in the following Table.

DETD 8. Entrapment of aspartase in **sol-gel glasses**.

DETD . . . disrupted by sonication. The homogenate was cleared by centrifugation (10,000.times.g, 30 min, 4.degree. C.) and used for the preparation of **sol-gel glasses**. The homogenate (0.5 ml) was mixed with NaF solution (0.2 ml) at the concentrations indicated in the Table below. Methanol. . .

DETD 9. Preparation of protein-doped **glasses** by NaOH catalyzed polycondensation. Immobilization of alkaline phosphatase.

DETD . . . pathological conditions, and may thus be of significant prognostic value. We have used an Anti-IL-2R monoclonal antibody, trapped in a **sol-gel** glass, to determine IL-2R, using a sandwich immuno assay test (cell-free Interleukin-2 Receptor CK 1020, 96 Test kit, T Cell Sciences, Inc., Cambridge, Mass., USA). Trapping of Anti-IL-2R monoclonal antibody in a "**sol-gel**" glass was carried out with a starting solution composed of methanol (3 mi), TMOS (2.5 ml), 6 mM phosphate buffered. . .

CLM What is claimed is:

1. A reactive **sol-gel** comprising a porous gel containing a cell-free dopant of biological origin trapped therein and formed by non-denaturing polymerization of at least one monomer of the formula M(R).sub.n (P).sub.m and selected from the group consisting of **metal** alkoxides, semi-**metal** alkoxides, **metal** esters and semi-**metal** esters, wherein M is a metallic or semi-metallic element, R is a hydrolyzable substituent, n is an integer of 2 to 6, P is a non-polymerizable substituent and m is an integer of 0 to 6, and optionally an **organic** monomer, under acidic, neutral or basic conditions and in the presence of a dopant, said polymerization including a gelling step. . .

2. A reactive **sol-gel** as defined by claim 1, wherein the porous gel is in the form of a thin film or an array. . .

3. A reactive **sol-gel** as defined by claim 2, wherein the thin film is a molecular monolayer.

4. A reactive **sol-gel** as defined by claim 2, wherein the thin film is a macroscopic layer.

5. A reactive **sol-gel** as defined by claim 2, wherein the thin film is supported on a solid support including an optical material.

6. A reactive **sol-gel** as defined by claim 1, wherein the porous gel is in the form of thin sieves.

7. A reactive **sol-gel** as defined by claim 1, wherein at least two dopants are trapped in the porous gel and wherein the dopants. . .

8. A reactive **sol-gel** as defined by claim 1, wherein the distribution of the dopant in the gel is nonhomogeneous and follows a predetermined. . .

9. A reactive **sol-gel** as defined by claim 1, wherein the cell-free dopant of biological origin is selected from the group consisting of enzymes,. . .

L6 ANSWER 16 OF 22 USPATFULL

AN 94:20235 USPATFULL

TI Doped **sol-gel glasses** for obtaining chemical interactions

IN Avnir, David, Jerusalem, Israel
Ottolenghi, Michael, Jerusalem, Israel
Braun, Sergei, Jerusalem, Israel
Zusman, Riyka, Jerusalem, Israel
PA YISSUM, Research Development Company of the Hebrew University of Jerusalem, Jerusalem, Israel (non-U.S. corporation)

PI US 5292801 19940308
AI US 1992-937258 19920831 (7)
RLI Division of Ser. No. US 1991-637873, filed on 8 Jan 1991
PRAI IL 1990-93134 19900123
DT Utility
FS Granted
LN.CNT 592
INCL INCLM: 525/054.100
INCLS: 422/055.000; 422/056.000; 422/057.000; 435/174.000; 435/175.000; 435/176.000; 436/008.000; 436/183.000; 501/012.000; 501/032.000
NCL NCLM: 525/054.100
NCLS: 422/055.000; 422/056.000; 422/057.000; 435/174.000; 435/175.000; 435/176.000; 436/008.000; 436/183.000; 501/012.000; 501/032.000
IC [5]
ICM: C08G063-48
ICS: B01D053-00; G01N021-00; G01N033-00
EXF 525/54.1; 514/2; 514/21; 530/402; 530/403; 530/405; 530/408; 530/409; 530/811; 435/174; 435/175; 501/12; 501/32

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Doped **sol-gel glasses** for obtaining chemical interactions

AB A method is proposed of obtaining a chemical interaction between at least one reagent trapped in **sol-gel** glass by doping it with the reagent, and diffusible solutes or components in an adjacent liquid or gas phase. The reagents, the solutes or the components can be any **organic** or inorganic compounds or materials of biological origin including enzymes. The doped **sol-gel** glass in various forms may be useful as analytical test, chromatographic medium, sensor, catalyst or biocatalyst, electrode or enzyme electrode,. . .

SUMM . . . solid support and diffusible solutes or components in an adjacent liquid or gas phase, wherein the reagent is trapped in **sol-gel** glass (hereinafter also referred to as doped **sol-gel** glass) which provides the solid support to the reagent.

SUMM The method according to the present invention can be applied to a variety of interactions between the doped **sol gel glasses** and reagent in an adjacent liquid or gas phase. The present invention can be useful in a myriad of applications:. . . useful for detection of ions by chemical interaction between the ions in an aqueous phase and reagents trapped in the "**sol-gel** " glass, or vice versa, via characteristic "color test" reactions, or other routine detection methods. Another example is utilization of the. . .

SUMM The method can be applied as well for medical diagnostic purposes e.g. for detecting inorganic ions or small **organic** molecules in blood, urine and other body liquids. Another example, according to the present invention, is a chemical interaction between a substrate or antigen in the liquid phase and an enzyme or antibody trapped in the " **sol-gel**" glass.

SUMM For centuries, inorganic **glasses** have been prepared by high temperature melting methods. This has imposed a major limitation upon the technological application of **glasses**: additives were restricted to thermally stable inorganic materials, while precluding the incorporation of labile **organic** molecules.

SUMM A recent major development in material science has been the preparation of inorganic (silica) **glasses** through the low temperature " **sol-gel" synthesis** as disclosed by (Brinker, C. J., Scherer, G. W., **Sol-Gel** Science, Academic Press, San Diego (1990). An amorphous bond network of the glassy material is prepared by the room-temperature polymerization of suitable monomers, usually **metal** alkoxides, according to schemes such as:

SUMM By **sol-gel** glass one also means the product obtained by a polymerization of **metal** alkoxide mixtures which bear both hydrolyzable and nonhydrolyzable substituents.

SUMM The low-temperature glass **synthesis** allows doping of inorganic (silica or other) **glasses**, with essentially any **organic** molecule. This possibility was used for trapping of photoactive molecules by adding the compound to the starting mixture at the. . . R., J. Phys. Chem. 88, 5956 (1984)). The compound remained permanently trapped, i.e. non-leachable system have been obtained. These doped **sol-gel glasses** have been used as photoactive materials, such as:

SUMM (d) Photochromic and phosphorescent **glasses**.

SUMM . . . such parameters as porosity, water content and degree of (cage) polarity (Kaufman, V. R., Avnir, D., Structural changes Along the **Sol-Gel**-Xerogel Transitions, Langmuir 2, 717 (1986); Kaufman, V. R., Avnir, D., Pines-Rojanski, D., Huppert, D., Water Consumption During the Early Stages of the **Sol-Gel** Polymerization, J. Non-Cryst. Solids 99, 379 (1988)).

SUMM **Sol-gel glasses** demonstrate several technologically attractive properties:

SUMM Surprisingly, it was found that molecules trapped in **sol gel glasses**, may interact with diffusible solutes or components in an adjacent liquid or gas phase in the pore space. This finding opened a new wide range of applications of doped **sol-gel glasses** as solid media for chemical interactions.

SUMM . . . least one diffusible solute or component in an adjacent liquid or gas phase, wherein the reagent is trapped in the **sol-gel** glass which serves as the solid support. The reagent can be any **organic** organometallic, or inorganic compound, or any biological material capable of being trapped in the **sol-gel** glass.

SUMM The diffusible solute or components can be any **organic** compound, stable **organic** radical, organometallic compound, or inorganic compound or biological material capable to interact with the trapped reagents.

SUMM . . . present invention can take place between anions or cations in a liquid or gas phase and reagents trapped in the **sol gel** glass or vice versa. For example the interaction may take place between **metal** ions and a specific reagent via a characteristic colour-test reaction, as in: (1) the determination of Fe.sup.+2 cation with o-phenanthrolin,. . . one of the many examples for a pH sensors. The analytical test can be carried out by dipping the doped **sol gel** glass in the solution and observing the resulting color change.

SUMM The **sol gel** glass according to the present invention can be in any shape suitable for the test. For example it can have. . . inert solid support. Thus, an electrochemical test according to the invention can be performed by preparing electrodes coated with doped **sol gel** glass layers. These electrodes may be used for clinical, analytical or industrial purpose, or as biosensors.

SUMM . . . quantitative analysis of pollutants. The pollutants may be for example chlorides, nitrates, phosphates, herbicides, insecticides, inorganic ions and pollutants of **organic** origin. Detection devices according to this invention can be utilized as part of

continuous monitoring systems.

SUMM The present invention can be utilized for extracting or separating molecular solutes from liquid solutions. The doped **sol gel glasses** can be used according to the present invention for all chromatographic purposes, including liquid, gas and thin layer chromatography. The extraction or separation is performed by passing the solution through columns made from appropriately doped **sol gel** material. The thin layer chromatography according to this invention can be performed on conventional glass plates, paper or other inert solid support coated with doped **sol -gel** glass layers.

SUMM Medical diagnostic is another application of the present invention. For example, detection of inorganic ions, small **organic** molecules and other components in blood, urine and other body liquids can be made. The invention can be applied also. . .

SUMM . . . present invention relates, as well, to a method for preparation of bioactive materials (biocatalysts) by entrapment of enzymes in forming **sol-gel** glass, which, following polycondensation of suitable monomers, serves as a solid matrix, bonding the enzyme and conveying to it mechanical,. . .

SUMM . . . according to the present invention, can be applied to a variety of enzymes or enzyme systems, including co-immobilization of co-factors, **organic** and inorganic ligands, mono- and polyclonal antibodies, and their detection systems.

SUMM . . . the present invention can be useful in a variety of applications, such as: (a) biochemical reactions and other bioconversions in **organic** and inorganic solvent solutions, (b) detection or qualitative determination of **organic** and inorganic molecules, which are substrates of the immobilized enzymes, or inhibitors, or modifiers of enzyme activity, (c) construction of. . .

SUMM Several properties of the **sol-gel glasses** make them especially attractive as possible enzyme catalyst supports: (a) the ability to entrap large amounts of additives; (b) the. . .

SUMM . . . therefore also to a method for obtaining bioactive materials based on enzyme molecules trapped within the porous structure of a **sol-gel** glass. The entrapment is achieved by the addition of a cell-free enzyme to a mixture of monomer or monomers at. . .

SUMM Unexpectedly, we have found (1) that proteins can be trapped within the matrix of a forming **sol-gel**, (2) that several cell-free enzymes, belonging to various classes: hydrolases, oxidoreductases, lyases and the like, can be effectively entrapped in such composite bioactive **sol-gel glasses**, while retaining high enzymatic activity, and (3) that strong binding forces retain the enzyme in the matrix, thus producing a. . .

SUMM The **sol-gel** immobilized enzymes may be used as biosensors for hormonal tests or for any industrial purposes, including diagnostic and synthetic purposes. Said enzymes can be doped in **sol gel** glass layers coated on electrodes for probing any substrate. The enzymatic interaction according to the present invention can be applied also to radioactive tests and also for enzymatic column chromatography (crushed powder **sol gel glasses** may be used as support for enzymatic column chromatography).

SUMM The **sol gel** glass can be applied, according to the present invention, as active specific membranes allowing selective incorporation of the trapped molecules. . .

SUMM The present invention relates also to the application of doped **sol gel glasses** according to this invention as well as for the preparation of **sol gel glasses** and doped **sol gel glasses** for such applications.

SUMM When prepared as a thin film, the width of the **sol gel** glass may be from molecular monolayers up to macroscopic layers. The thin film can be part of a multi-layered array of thin films. The **glasses** may be supported on an electrode or optical support.

SUMM The unique transparency of **"sol gel" glasses** in the range above 250 nm, makes them highly applicable to quantitative spectrophotometric and spectrofluorimetric tests. Trapping of host molecules. . . require specific synthetic methods such as those associated with covalent linking of reagents to solid supports. Moreover, inherent properties of **sol gel glasses** such as high surface area, the wide range of available pore sizes and the thin film technology, make them highly. . .

DRWD The FIGURE Drawing shows various **sol-gel glasses** with a reagent trapped therein, both before and after reaction with a component in a liquid phase.

DETD A. Preparation of doped **"sol-gel" glasses**

DETD The polycondensation of **alkoxysilanes** is associated with gelation of the sol, which after drying is densified by a mild heat treatment to form a. . . final glass are determined by the chemical and physical conditions during the process of preparation. They depend upon the ratio **metal** (e.g. silane)/alcohol/water, the alkoxide pH, the presence of a catalyst, the temperature, the drying time and the amounts of **organic** additives, such as surface active agents.

DETD 1. A standard mixture for preparation of doped **"sol-gel" glasses** contained TMOS (5 ml) H.sub.2 O (2.4 ml) and methanol (6. ml). The appropriate catalyst and the desired reagent were. . .

DETD 2. An alternative technique of preparing **sol-gel glasses** is based on thin-layer coating of conventional glass supports. A characteristic procedure for the preparation of such thin layers began. . .

DETD B. Representative examples of reactivity of reagents trapped in **sol-gel glasses**

DETD . . . 1, arrows denote transitions from the reagent-doped glass to the same glass after immersion in the tested solution. The doped **glasses** represent four classes of reactions: (a) a glasstrapped **organic** reagent with an inorganic cation to be determined in the solution; (b) same with inorganic anions; (c) a glass doped with an inorganic ion, testing a solution containing an **organic** molecule (reversal of a & b); (d) glass doped with a pH indicator.

DETD Middle: Doped **glasses** (top) and some **glasses** after immersion in solutions containing several ions:

DETD 1. Preparation of **sol-gel** immobilized enzymes.

DETD . . . samples containing PEG 400, the polymerization was completed in about 3 h. All the liquid remaining on the top of **sol-gel** was then removed by suction. In methanol-containing mixtures gelation took place in about 4-5 h. The polymerized sol was allowed. . .

DETD 2. Retention of protein by the **sol-gel** glass.

DETD All the **glasses** prepared according to example C1 were ground to a size of about 60-100 mesh and packed in 2 ml-columns. The. . .

DETD 3. Entrapment of trypsin in **sol-gel glasses**

DETD Trypsin (E.C. 3.4.21.4, from bovine pancreas, 11,000 U/mg) was supplied by RAD Chemicals, Rehovot, Israel. Trypsin entrapped in **sol-gel** was prepared as described in example C1. Assays were performed on the washed **glasses** at 25.degree. C. at pH 8 using N-benzoyl-L-arginine-4-nitroanilide (3.3 mM) as the substrate. The concentration of NaF in the enzyme. . .

DETD 4. Entrapment of acid phosphatase in **sol-gel glasses**. Acid phosphatase (E.C. 3.1.3.2, from wheat germ, 0.45 U/mg) was purchased from Sigma. The acid phosphatase-containing

**sol-gel glasses** were prepared as described in the example C1. The assays were performed on the washed **glasses** at 25.degree. C. at pH 5.6 using p-nitrophenyl phosphate (6 mM) as the substrate. The activity yield, calculated in percents of enzyme activity used initially for the preparation of **glasses**, is shown in the following Table:

DETD 5. Thermal stability of immobilized acid phosphatase in different **sol-gel glasses**.

DETD The acid phosphatase-containing **sol-gel glasses** (example C4) were incubated at 70.degree. C. in citrate buffer (pH 5.6, 0.1M) for various periods of time (up to. . .

DETD 6. Entrapment of peroxidase in **sol-gel glasses**.

DETD . . . 200 U/mg) was obtained from Sigma. Sol-gels doped with peroxidase were prepared as shown in the example C1. All the **glasses** prepared with the addition of PEG 400 were active, although it was not possible to determine the extent of their. . . of the assay mixture indicated improved activity yields at higher concentrations of PEG 400. In contrast to trypsin and catalase, **sol-gel glasses** made at elevated concentrations of NaF were more active. **Glasses** prepared in methanol-containing mixtures were devoid of peroxidase activity.

DETD 7. Entrapment of trypsin in **sol-gel glasses**.

DETD . . . to reach the room temperature. The polymerized sol was allowed to dry for a week at 30.degree. C. The resulting **glasses** were treated as described (example C2). Trypsin activity of the trypsin-doped **sol-gel glasses** expressed as the yield of activity used for the preparation of the catalyst is presented in the following Table.

DETD 8. Entrapment of aspartase in **sol-gel glasses**.

DETD . . . by sonication. The homogenate was cleared by centrifugation (10,000 xg, 30 min, 4.degree. C.) and used for the preparation of **sol-gel glasses**. The homogenate (0.5 ml) was mixed with NaF solution (0.2 ml) at the concentrations indicated in the Table below. Methanol. . .

DETD 9. Preparation of protein-doped **glasses** by NaOH catalyzed polycondensation. Immobilization of alkaline phosphatase.

DETD . . . pathological conditions, and may thus be of significant prognostic value. We have used an Anti-IL-2R monoclonal antibody, trapped in a **sol-gel** glass, to determine IL- 2R, using a sandwich immuno assay test (cell-free Interleukin-2 Receptor CK 1020, 96 Test kit, T Cell Sciences, Inc., Cambridge, Mass., USA). Trapping of Anti-IL-2R monoclonal antibody in a "**sol-gel**" glass was carried out with a starting solution composed of methanol (3 ml), TMOS (2.5 ml), 6 mM phosphate buffered. . .

CLM What is claimed:

1. A process for the preparation of a reactive **sol-gel** glass, comprising polymerizing at least one monomer of the formula M(R).sub.n (P).sub.m and selected from the group consisting of **metal** alkoxides, semi-**metal** alkoxides, **metal** esters and semi-**metal** esters, wherein M is a metallic or semi-metallic element, R is a hydrolyzable substituent, n is an integer of 1 to 6, P is a non-polymerizable substituent and m is an integer of 0 to 6, and optionally an **organic** monomer, under acidic, neutral or basic conditions and in the presence of a dopant to form a porous xerogel containing. . . and a drying step conducted at not greater than 45.degree. C., said dopant being selected from the group consisting of **organic** compounds, stable **organic** radicals, organometallic compounds, inorganic compounds and molecules of biological origin, the dopant being reactive after preparation of the

xerogel.

2. A process as defined by claim 1, wherein M is at least one **metal** selected from the group consisting of Si, Al, Ti and Pb, R is at least one substituent selected from the. . .
3. A process as defined by claim 1, wherein the **sol-gel** glass is formed from at least two monomers of the formula M(R).sub.n.

4. A process as defined by claim 1, wherein dopant molecules are trapped in the **sol-gel** glass.

L6 ANSWER 17 OF 22 USPATFULL
AN 93:107111 USPATFULL
TI Fast **sol-gel** preparation of **glasses**
IN Haruvy, Yair, Austin, TX, United States
Webber, Stephen E., Austin, TX, United States
PA Board of Regents, The University of Texas System, Austin, TX, United States (U.S. corporation)
PI US 5272240 19931221
AI US 1991-707140 19910529 (7)
DT Utility
FS Granted
LN.CNT 1492
INCL INCLM: 528/010.000
INCLS: 528/012.000
NCL NCLM: 528/010.000
NCLS: 528/012.000
IC [5]
ICM: C08G077-06
EXF 528/10; 528/12
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Fast **sol-gel** preparation of **glasses**
AB The present invention relates to a method of preparing **glasses** from **metal** alkoxides. **Glasses** are crack-free and prepared rapidly in a single step. Optically clear polysiloxane **glasses** as thin films may be prepared in a matter of minutes. A glow discharge curing method is disclosed which rapidly. . . crack-free multiple-layered films may be prepared by the disclosed method which can be modified according to desired properties of the **glasses**.
SUMM The invention relates generally to **sol-gel** **glasses** and a chemical procedure for their preparation. Preferred "crack-free" **glasses** are polymerized from substituted **metal** alkoxides having two or three hydrolyzable groups. Thin films up to 100 .mu. are typically obtained in a rapid single. . .
SUMM **Sol-gel** techniques have been extensively investigated for more than two decades (Gottardi, 1982) and used to prepare **glasses** and ceramics for use in a wide variety of applications, employing various precursors, catalysts, additives and procedures. **Sol-gel** precursors most investigated have been prepared from siloxanes, especially tetraalkoxysilanes (Reisfeld, 1987). Titania, alumina (Kobayashi, 1988) and mixed **glasses** have also been investigated. Numerous chromophores have been incorporated into **sol-gel** produced glassy materials, laser-dyes in particular. The latter have exhibited promising characteristics for use in nonlinear optics (NLO), especially for laser systems (Reisfeld, 1989). Dye-embodying supported glass thin films have been prepared by **sol-gel** techniques, aiming at surface laser systems (Kobayashi, 1988), yet prolonged and complex

processes are required to facilitate crack-free **glasses** of the desired properties.

SUMM Tetraethoxysilane is the favored precursor for the preparations of pure silica (SiO.sub.2) **glasses** by the **sol-gel** method due to its moderate reaction rate. The water-to-siloxane molar ratios (MR) most commonly employed is 5:1 to 10:1. A co-solvent (e.g. ethanol) is regularly added to maintain a one-phase reaction solution, although it was recently demonstrated, in the **sol-gel** reaction of tetramethoxysilane, that the methanol produced by the hydrolysis was sufficient to maintain a single-phase at an early stage. . .

SUMM . . . encaging large molecules (e.g. chromophores, enzymes) which have been introduced into the reaction mixture. However, during this stage of the **sol-gel synthesis** severe cracking and fragmentation of the formed glass are the common obstacles that impede the fabrication of articles and films. . . Many investigators have attempted to overcome this obstacle by using a wide variety of additives such as dimethylformamide (DMF), formamide, **organic** acids or surfactants. Even with these additives, however, an extremely slow and very cautious drying of the **sol -gel** glass is necessary for the survival of a fracture-free glass, making this synthetic route more of an art than a. . .

SUMM The cracking problem is further aggravated where **sol-gel glasses** are cast onto a rigid support since the gelling matrix is no longer free to contract. Crack-free supported glass-films can. . .

SUMM Although crack-free **glasses** from sol-gels have been prepared, the procedures are time-consuming and often complex. Of particular concern from a practical aspect is. . .

SUMM . . . which can be made as single or multiple layer thin films with a range of thicknesses. Thin films polymerized from **metal** alkoxide monomers are free of cracks and generally may be prepared in a few hours by curing at elevated temperatures.. . . glow discharge technique during the curing process. Guest molecules, including laser dyes and donor-acceptor molecules, are readily incorporated into the **glasses** produced by methods in accordance with the invention.

SUMM The invention is generally directed to a method of rapid preparation of crack-free **glasses**. A suitable **metal** alkoxide monomer is selected, polymerized during a hydrolysis step and subsequently cured. The inventors have discovered that through use of. . .

SUMM Suitable monomers for polymerization include **metal** alkoxides such as silane alkoxides, barium, yttrium, copper or aluminum alkoxides, titanium alkoxides or alkoxides selected from other **metal** groups as well as mixtures of the aforementioned **metal** alkoxides. Similarly, single **metal** alkoxide oligomers or mixed **metal** alkoxide oligomers may be used. Suitable substituted alkoxides include, for example, methyl trimethoxysilane, dimethyl dimethoxysilane, ethyl triethyloxysilane and so forth.. . . resulting polymer glass will depend on te structure of the monomer. Methyl trimethoxysilane can be used to provide polymethylsiloxane (PMSO) **glasses**. In order to obtain **glasses** with desirable mechanical properties, such as rigidity, flexibility or toughness, the monomer selected preferably has two or three hydrolyzable groups.. . . dimethoxy silane monomers with hydrogen in the remaining position(s), e.g., SiH(OMe).sub.3, to be used, resulting in virtually pure silicon oxide **glasses**.

SUMM Hydrolysis of the selected monomer is preferably accomplished at an elevated temperature. Although optically clear **glasses** have been obtained when hydrolysis of **alkoxysilanes** is conducted at room temperature or temperatures up to 60.degree. C., phase separation may frequently occur during the hydrolysis stage.. . .

SUMM . . . from monomers such as alkoxy substituted silanes by processes similar to the aforementioned methods have traditionally been referred to as **sol-gel glasses** or sol-gels. In fact, the formation of polymers described in the present invention are formed mainly by polymerization rather than a sol aggregation. It is therefore understood that references to **sol-gel** methods or to sol-gels are not intended as a limitation on the characterization of the **glasses** or thin films prepared by the aforementioned methods.

SUMM . . . while it crosslinks. There is a significant decrease in volume and dimensions taking place during the drying stage of the **sol -gel** derived glass resulting in extensive fractures. This problem is overcome by minimizing the volume of the reactants, illustrated for example. . .

SUMM . . . the base protonation reaction is reversed. The volatile amine is expelled from the reaction, thus slowing the reaction rate. Polymethylsiloxane **glasses** incorporating Pyridin-1 laser dyes prepared using dimethylamine catalysis which were cast onto supports and dried similarly to those prepared by. . . as those found with acid catalysis. Thus both types of catalysis, acid and base, may be used to prepare crack-free **glasses** and in some cases either type of catalyst may be used.

SUMM One hydrolysis product of **metal** alkoxide monomers is an alcohol. When trimethoxysilane monomers are used this product is methanol, whereas if ethoxy substituents are present. . .

SUMM Curing of a hydrolyzed/polymerized **metal** alkoxide monomer may be accomplished in situ or subsequent to a forming process such as casting. Thus in a further. . . cast onto substrates. Such substrates may include rigid or flexible surfaces such as glass, metals, or flexible or inflexible polymers. **Sol-gel glasses** formed on rigid supports are apt to cause problems due to the formation of cracks during the curing process as. . .

SUMM . . . surfactant at relatively high concentrations, for example up to 3% in the final glass. However, surfactant embodied in the final **glasses** may decompose when employed for high energy density applications, for example for solid state lasers, adversely affecting performance. However, the inventors have discovered that the new method of preparing **metal** alkoxide polymers provide solutions particularly amenable to spin-casting without addition of additives such as surfactants, DMF or similar drying control. . .

SUMM . . . cracks as well as propagation of existing ones, thus allowing a healing process to occur. Additionally, by carrying out the **sol -gel** reaction and the spin-casting process under inert atmosphere such as nitrogen, argon, or other inert gases, most of the early. . . not necessary with ethoxy substituted silane monomers. Yet by using all three to prepare films using trimethoxysilane monomer, crack-free polysiloxane **glasses** may be obtained after curing for only a few hours at ambient temperature under an inert atmosphere.

SUMM It will be appreciated that the water to monomer ratio, that is the MR ratios, in polymers used to prepare **glasses** may be optimized or tuned to allow fast polymerization while minimizing crosslinking. By optimization or tuning is meant adaptations of. . .

SUMM A further aspect of the invention includes **glasses**, thin films, and multiple-layered films or **glasses** prepared by the aforedescribed methods.

SUMM . . . of polyimides. Curing at room temperature has been accomplished in short periods, often as short as 10-20 min for polymethylsiloxane **glasses** and as short as 60 min for polyamic acid resins. Thin films up to 100 micrometers have been rapidly cured. . .

SUMM Glow-induced **sol-gel** curing may result in the formation of a hydrophilic surface on the polymer film. Without application of glow discharge, polymer. . .

SUMM Additionally, multilayered assemblies of hydrophilic **sol-gel** films may be prepared by glow discharge curing. Hydrophilic gel surfaces will stick together better than hydrophobic gel surfaces and. . .

SUMM Curing of the hydrolyzed/polymerized **metal** alkoxide monomer may be carried out by allowing the polymerized solution to "air-cure" by standing at ambient or elevated temperature. . .

SUMM . . . as Rhodamine-6G, Pyridin-1, or Coumarin-153 Where high concentrations of guest molecules within the matrix are desired certain modifications of the **sol-gel** polymerization process have been found desirable. Thus it is preferred to slow evaporation of the alcohol, methanol for example arising from methoxyl group hydrolysis, in the **sol-gel** until sufficient molecular weight and viscosity have been obtained. This may be conveniently carried out by conducting the first 5. . . methods of slowing down or counteracting fast evaporation of methanol from the polymerization solution include adding less volatile solvents, miscible **organic** solvents such as ethanol, higher alcohols, acetonitrile, or the like, or water immiscible **organic** solvents such as toluene.

SUMM Films prepared b the aforedescribed methods, particularly polymethylsiloxane and polysiloxane films, are useful as optically clear **glasses** or may be used as waveguides, particularly multilayered assemblies, for example, by incorporating laser dyes into the monomer solutions used. . .

DRWD FIG. 2 shows a typical set-up for hydrolyzing and polymerizing **metal** alkoxy monomers used to prepare **glasses** and thin films. 1 is a water bath at constant temperature; 2 are hollow beads; 3 is a styrofoam bar;. . .

DRWD FIG. 3 is a FTIR spectrum of **sol-gel** (MTMS) prepared polymethylsiloxane thin-film on an aluminum support.

DETD The present invention is a rapid, single-step method of preparing what are commonly known as **sol-gel glasses**, supported films in particular. The invention is illustrated in detail with preparation of **glasses** prepared from alkoxysilane and alkylalkoxysilane monomers and indicates variations which allow flexibility in achieving desired polymer properties, depending on the application. Especially desirable are fracture or crack-free **glasses** that are rapidly prepared, some in a matter of minutes.

DETD Although the method may be varied, the inventors have shown that preparation of crack-free **glasses** from methyl alkoxysilane monomers depends on the maintenance of a single phase during the hydrolysis/polymerization process. Thus the practitioner will. . .

DETD . . . when the monomer is mixed with water that certain precautions are taken to assure even polymerization and subsequent grainless, crack-free **glasses** after drying. Trimethylsilane is mixed with water at a MR of about 0.95 under an inert atmosphere such as nitrogen,. . .

DETD **Glasses** are generally formed after hydrolysis/polymerization followed by a curing process. Curing entails several reactions, usually some hydrolysis, further polymerization and formation of crosslinks. For many siloxane **glasses**, particularly films, formed from alkoxy or alkylalkoxy monomers, curing at room temperature or elevated temperatures will provide satisfactory crack-free films.. . .

DETD . . . rapid curing by glow discharge. Siloxane films prepared by spin-casting trimethylsilane monomer are optically clear and virtually identical to SiO.sub.2 **glasses** after curing. While glow discharge may not be desirable for acceleration of curing in these films, it could be used. . .

DETD Donor-acceptor molecules incorporated in the **sol-gel** matrices were p-nitroaniline (PNA), and 4,4'-diamino-diphenyl sulfone (DDS) from Aldrich (AR) and 4,4'-dimethylamino nitrostilbene (DANS) from

Kodak.

DETD Preparation of the Support **Glasses**

DETD Multilayered Polymethylsiloxane **Glasses**

DETD . . . several layers of PMSO on a support according to the procedure of Example I resulted in a multilayered assembly. The **sol-gel** and drying processes of a single-layer was applied in a straight-forward manner to the preparation of a multilayered assembly (1".times.1"). . .

DETD TABLE 1

HTMS Fast **Sol-Gel** Experiments. a. Ambient Atmosphere

| No. | wt/wt H.sub.2 O/HTMS.sup.(a) mol/mol | HCl (M).sup.(b) | Temp. (deg C.) | Results and Observations |
|---|---|---|---|---|
| 1 | 0.22 | 1.5 | 10.sup.-2 | 70 Gelling. . . |

DETD TABLE 2

HTMS Fast **Sol-Gel** Experiments. b. Inert Atmosphere

| No. | wt/wt H.sub.2 O/HTMS.sup.(a) mol/mol | Atm. | S C.sup.(f) | Temp. (deg C.) | Results and Observations |
|---|---|---|---|---|---|
| 13 " | 0.95 | N.sub.2 | ;. | . . | |

DETD TABLE 3

Cracking Duration of **Sol-Gel Glasses** Prepared from TMOS-DMDMS Mixtures.sup.(a)

| TMOS (mol. %) | DMDMS (mol. %) | No. --OMe (average) | Time.sup.(b) before cracking (h) |
|---|---|---|---|
| 100 | 0 | 4.0 | <1 |
| 75 | 25 | 3.5 | 12 |
| 67. . . | | | |

DETD . . . indicated that minimization of the volume of the reactants and the cast sol leads to elimination of cracking in the **glasses** produced.

DETD TABLE 4

Calculated Contraction for SiO.sub.2 Glass Prepared by the **Sol-Gel** Technique

| Reactants | SiO.sub.2 Weight Fraction | Volume.sup.(a) Contraction | Longitudinal Contraction |
|---|---|---|---|
| One-phase Si(OEt).sub.4 /H.sub.2 O/MeOH | 0.13 | 7.6 | 2.0 |
| 1:5:5 (m/m) Two-phase | | | |

Si(OEt).sub.4 /H.sub.2 O
0.20 5.0 1.7
1:5 (m/m)
Si(OMe).sub.4. . .
DETD Less detachment occurred in **glasses** cast on base-washed supports compared to acid-washed supports. The results may be explained by increased adherence of the film to. . .

DETD TABLE 5

**Sol-Gel** Experiments and Observations Under Acid Catalysts.sup.(a)

| REACTION CONDITIONS Monomer | Water Ratio (m/m) | Temp (.degree.C.) | Ph.M.sup.(b) min | Cracking (hours).sup.(c) | Clarity | Remarks |
|---|---|---|---|---|---|---|
| Si(OEt).sub.4 | 5.7. . . | | | | | |

DETD Results indicated that methyltrimethoxysilane monomer could be used at MR as low as 1:1, in contrast to **sol-gel** reactions of TEOS. Phase-merging of the reactants was typically observed within a few seconds even at room temperature and the. . .

DETD As shown in Table 5,the MTMS **sol-gel** reactions were carried out at a temperature range of 25.degree.-60.degree. C. At the higher temperatures, more vigorous hydrolysis was observed and gelation occurred more quickly. A short time after casting, all the **glasses** developed a milky opaque surface. By elevating the temperature to nearly 80.degree. C. during hydrolysis and polymerization, more even hydrolysis. . .

DETD Embodiment of guest molecules in the **sol-gel** matrix was accomplished by incorporating guest molecules (e.g. laser dye) in the reaction mixture and proceeding according the regular fast **sol-gel** procedure of Example 1. Generally, this resulted in dye-embodying glass-films, usually with a marginal effect on the fast-**sol-gel** process itself.

DETD . . . these laser dyes, as well as embodied laser dyes of larger molecular weight (>600) were attained with the same fast **sol-gel synthesis** by increased acid concentration. Embodying of discrete Pyridin-1 species was attained at dye loading of 0.5-1 mg/g monomer. Loadings smaller. . .

DETD Donor-acceptor type molecules such as PNA and DDS are embodied in the PMSO **glasses** by the same fast **sol-gel** process of Example 1 as laser dyes. Higher loadings (10-15%) of these chromophores were prepared with the same fast **sol-gel synthesis** and again, an increased concentration of acid was required to retain the fast rate and the good optical quality of. . .

DETD **Metal** ions (e.g. Cu, Ti, Ce, A) were easily incorporated into the fast **sol-gel** recipe. However, most **metal** ions tended to induce aggregation of PMSO particles, resulting in a grainy appearance. Therefore, their incorporation (as aqueous solution of their salt, at the typical loading of 2 mg/g MTMS) was preferably done when the **sol-gel** process was almost completed, and additional polymerization was allowed for a few seconds only. The spin-casting was immediately carried out before in-vial gelation or aggregation could take place. The resulting glass had the typical coloration and absorbance of the **metal** salt as well as the optical clarity of the PMSO glass.

DETD High concentrations of donor-acceptor molecules were difficult to embody

in a **sol-gel** glass matrix because these compounds generally exhibited little miscibility in the siloxane monomer due to their polar nature. This problem. . .

DETD . . . to keep the solution precipitate-free until sufficient molecular weight and viscosity had been attained, sufficient methanol was kept in the **sol-gel** until the casting stage. This was accomplished by carrying out the first five min of polymerization in a sealed vial,. . .

DETD TABLE 6

Absorbance and Fluorescence Maxima of Rh6G Laser Dye in **Sol-Gel Glasses** and in Solution

| MEDIUM | ABSORBANCE MAXIMUM | FLUORESCENCE MAXIMUM |
|---|---|---|
| Ethanol | 530 | 580-600 |
| Silica glass (SiO.sub.2) | 525 | 572 |
| Polymethylsiloxane (PMSO) | 532 | 557 |
| Polyhydrogensiloxane (PHSO) | 524 | 558 |
| Polyhydrogensiloxane following oxidation | 524 | 564 |

DETD Inclusion of NLO molecules which carry amino-groups and substituted amino-groups, pyridine groups, etc. in **sol-gel** glass prepared by acid catalysis may face some difficulties if the guest molecules undergo some protonation. Among the laser dyes, Pyridin-1 is an example which requires additional measures if it is to be embodied in the **sol-gel** glass at high concentrations. It was desirable, therefore, to modify the new fast synthetic route and adapt it for basic. . .

DETD . . . at the interface of the phases with subsequent undergo rapid condensation and precipitation. Therefore, basic catalysts exhibiting higher miscibility in **organic** media were tested.

DETD Upon catalysis with dimethylamine (pK.sub.b .about.3.3 10.sup.-3 at 25.degree. C., fast and facile **sol-gel** reactions was maintained using concentrations between 10.sup.-2 to 4.4M. The higher compatibility of the **organic** base with both phases thus assists in their merging. In this respect, the **organic** base acted as a micro-surfactant. Further, this catalyst was volatile and upon consumption of most of the water, the base-protonation. . .

DETD . . . was expelled from the gel, thus slowing down the condensation. The later self-regulation phenomenon is of special importance for the **sol-gel** curing process: the more crosslinked the glass became, the more time was needed for stress relaxation processes. This relaxation period was extended by the catalyst evaporation and the consequent decrease of the condensation rate. Hence, **glasses** formed following casting onto a support behaved similarly to those prepared by the acid catalysis. All dyes investigated could be embodied in the **sol-gel** glass. Residual amines in the glass quenched the fluorescence of the glass-embodied dyes and therefore had to be removed from. . .

DETD . . . are comparable to data in the literature. In Table 7 the absorbance and fluorescence maxima in solution and in PMSO **glasses** prepared under acid and base catalysis are compared for the four laser dyes studied. The absorbance maxima in the glass. . .

DETD TABLE 7

Comparison of Absorbance and Fluorescence Maxima of Laser Dyes in **Sol-Gel** Glass and in Solution

| DYE | MEDIUM | ABSORBANCE MAXIMUM.sup.(c) | FLUORESCENCE MAXIMUM.sup.(c,d) |
|---|---|---|---|
| Rhodamine 6G | Ethanol | 530 | 581.sup.(e) (308) |
| | PMSO.sup.(a) | 532 | 557 (308) |
| | PMSO.sup.(b) | 536 | 525. . . |

DETD Multilayered Polymethylsiloxane **Glasses**

DETD . . . several layers of PMSO on a support according to the procedure of Example 1 resulted in a multilayered assembly. The **sol-gel** and drying processes of a single-layer was applied in a straight-forward manner to the preparation of a multilayered assembly of. . .

DETD Electric Field Curing of **Sol-Gel** Films

DETD **Sol-gel** films were prepared as described in Example 1 using methyltrimethoxysilane monomer except that accelerated curing was induced by application of. . .

DETD TABLE 8

Curing Time and Surface Properties of Glow Discharged **Sol-Gel** Films

H.sub.2 O/MTMS Molar Ratio.sup.(a)

| Voltage-Current-Time Glow Discharge Curing Sequence | Curing Time (min) | Contract Angle (aver:deg) |
|---|---|---|
| 2.25 | 10-12-2; 12-12.5-2; 13-15-2; 14-18-2; | <20. . . |

DETD TABLE 7

Typical **Sol-Gel** PMSO Recipes Loaded With Amino-Chromophores.sup.(a)

| Chromophore Loading Molar Ratio.sup.(b) | Water/PMSO Add. Solvent Add. 1M HCl (% w/w) | (% w/w) | Remarks |
|---|---|---|---|

PNA 35. . .

DETD 1. Proc. Int. Workshop, "**Glasses** and Glass Ceramics from Gels", Gottardi, V., Ed., J. Non. Cryst. Solids, vol. 48, 1982.

DETD 2. "**Sol-Gel** Technology for Thin films, Fibers, Preforms, electronics and Specialty Shapes", Klein, L. C., Ed., 1988, Noyes Publ., Park Ridge, N.J.

CLM What is claimed is:

4. The method of claim 1, 2, or 3 wherein the **metal** in the monomer is silicon, titanium, aluminum, barium, copper or yttrium.

11. The method of claim 1 wherein the **metal** alkoxide monomer is a trialkoxy-substituted.

12. The method of claim 1 wherein the **metal** alkoxide monomer is methyltrimethoxy-substituted.

13. The method of claim 1 wherein the **metal** alkoxide monomer is dimethyldimethoxy-substituted.

=>

FILE 'CAPLUS, BABS, CBNB, CEN, CIN, DKILIT, IFIPAT, JICST-EPLUS, PASCAL, PLASNEWS, PROMT, RAPRA, SCISEARCH, TEXTILETECH, USPATFULL, USPAT2, WPIDS, WTEXTILES' ENTERED AT 16:52:11 ON 28 JUL 2002

| | | |
|---|---|---|
| L1 | 76425 | S SOL(W)GEL |
| L2 | 6631 | S L1 AND GLASSES |
| L3 | 1062 | S L2 AND SYNTHESIS |
| L4 | 26 | S L3 AND ALKOXYSILANES |
| L5 | 23 | S L4 AND METAL |
| L6 | 22 | S L5 AND ORGANIC |